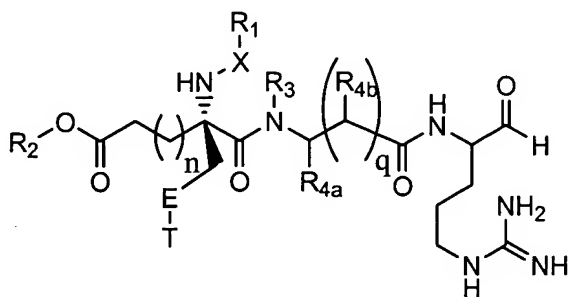


This listing of claims will replace all prior versions, and listings of claims in the application:

1. (Original) A compound of the formula:



(a) X is selected from the group consisting of -C(=O)-, -C(=O)-O-, -C(=O)NH-, -S(O)<sub>2</sub>-, -S(O)<sub>2</sub>NH- and a direct link;

(1) alkyl of 1 to about 12 carbon atoms which is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of Y<sub>1</sub> and Y<sub>2</sub>;

(2) alkyl of 1 to about 3 carbon atoms substituted with cycloalkyl of 3 to about 8 carbon atoms which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of Y<sub>1</sub>, Y<sub>2</sub> and Y<sub>3</sub>;

(3) cycloalkyl of 3 to about 8 carbon atoms which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of Y<sub>1</sub>, Y<sub>2</sub> and Y<sub>3</sub>; and

(4) aryl of about 6 to 14 carbon atoms which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of Y<sub>1</sub>, Y<sub>2</sub> and Y<sub>3</sub>;

(5) aralkyl of about 7 to about 15 carbon atoms which is unsubstituted or substituted on the alkyl chain with hydroxy or halogen and which is unsubstituted

or substituted on the aryl ring with 1 to 3 substituents selected from the group consisting of  $Y_1$ ,  $Y_2$  and  $Y_3$ ;

(6) hydrogen when X is  $-C(=O)NH-$ ,  $-S(O)_2-$ ,  $-S(O)_2NH-$ , or a direct link;

(7) heterocycloalkyl of 4 to about 10 ring atoms with the ring atoms selected from carbon and heteroatoms, wherein the heteroatoms are selected from the group consisting of oxygen, nitrogen, and  $S(O)_i$ , wherein i is 0, 1 or 2, which is unsubstituted or mono-, di-, or tri-substituted on the ring with 1 to 3 substituents selected from the group consisting of  $Y_1$ ,  $Y_2$ , and  $Y_3$ ;

(8) heterocyclo of 4 to about 10 ring atoms with the ring atoms selected from carbon and heteroatoms, wherein the heteroatoms are selected from the group consisting of oxygen, nitrogen, and  $S(O)_i$ , wherein i is 0, 1, or 2, including,



wherein is a 5 to 7 member heterocycle having 3 to 6 ring carbon atoms, where V is  $-CH_2-$ ,  $-O-$ ,  $-S(=O)-$ ,  $-S(O)_2-$  or  $-S-$ , which is unsubstituted or mono-, di-, or tri-substituted on the ring carbons with 1 to 3 substituents selected from the group consisting of  $Y_1$ ,  $Y_2$ , and  $Y_3$ ;

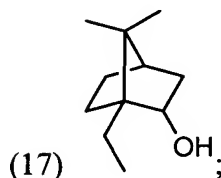
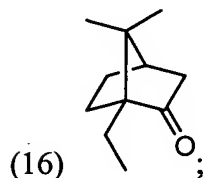
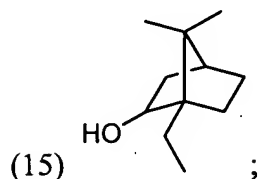
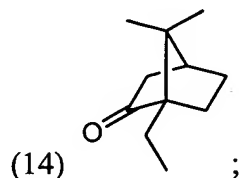
(9) alkenyl of 2 to 6 carbon atoms which is unsubstituted or substituted with cycloalkyl of 3 to 8 carbon atoms, which is unsubstituted or mono-, di-, or tri-substituted on the ring with 1 to 3 substituents selected from the group consisting of  $Y_1$ ,  $Y_2$ , and  $Y_3$ ;

(10) heteroaryl of 5 to 14 ring atoms with the ring atoms selected from carbon and heteroatoms, wherein the heteroatoms are selected from oxygen, nitrogen, and sulfur, and which is unsubstituted or mono-, di- or tri-substituted with 1 to 3 substituents selected from the group consisting of  $Y_1$ ,  $Y_2$ , and  $Y_3$ ;

(11) heteroaralkyl of about 5 to about 14 ring atoms with the ring atoms selected from carbon and heteroatoms, wherein the heteroatoms are selected from oxygen, nitrogen, and sulfur, which is unsubstituted or substituted on the alkyl chain with hydroxy or halogen and which is unsubstituted on the ring or mono-, di- or tri-substituted on the ring with 1 to 3 substituents selected from the group consisting of  $Y_1$ ,  $Y_2$ , and  $Y_3$ ;

(12) aralkenyl of about 8 to about 16 carbon atoms which is unsubstituted or mono-, di-, or tri-substituted on the aryl ring with 1 to 3 substituents selected from the group consisting of  $Y_1$ ,  $Y_2$ , and  $Y_3$ ;

(13) heteroaralkenyl of 5 to 14 ring atoms with the ring atoms selected from carbon and heteroatoms, wherein the heteroatoms are selected from oxygen, nitrogen, and sulfur, and which is unsubstituted or mono-, di- or tri-substituted on the ring carbons with 1 to 3 substituents selected from the group consisting of  $Y_1$ ,  $Y_2$ , and  $Y_3$ ;



(18) fused carbocyclic alkyl of about 9 to about 15 carbon atoms;

(19) difluoromethyl or perfluoroalkyl of 1 to about 12 carbon atoms;

(20) perfluoroaryl of about 6 to about 14 carbon atoms; and

(21) perfluoroaralkyl of 7 to 15 carbon atoms., and wherein each  $Y_1$ ,  $Y_2$ , and  $Y_3$  is independently selected and is (i) selected from the group consisting of halogen, cyano, nitro, tetrazolyl, guanidino, amidino, methylguanidino,  $-\text{CF}_3$ ,  $-\text{CF}_2\text{CF}_3$ ,  $-\text{CH}(\text{CF}_3)_2$ ,  $-\text{C}(\text{OH})(\text{CF}_3)_2$ ,  $-\text{OCF}_3$ ,  $-\text{OCF}_2\text{H}$ ,  $-\text{OCF}_2\text{CF}_3$ ,  $-\text{OC}(\text{O})\text{NH}_2$ ,  $-\text{OC}(\text{O})\text{NHZ}_1$ ,  $-\text{OC}(\text{O})\text{NZ}_1\text{Z}_2$ ,  $-\text{NHC}(\text{O})\text{Z}_1$ ,  $-\text{NHC}(\text{O})\text{NH}_2$ ,  $-\text{NHC}(\text{O})\text{NZ}_1$ ,  $-\text{NHC}(\text{O})\text{NZ}_1\text{Z}_2$ ,  $-\text{C}(\text{O})\text{OH}$ ,  $-\text{C}(\text{O})\text{OZ}_1$ ,  $-\text{C}(\text{O})\text{NH}_2$ , -

$C(O)NHZ_1$ ,  $-C(O)NZ_1Z_2$ ,  $-P(O)_3H_2$ ,  $-P(O)_3(Z_1)_2$ ,  $-S(O)_3H$ ,  $-S(O)_mZ_1$ ,  $-Z_1$ ,  $-OZ_1$ ,  $-OH$ ,  $-NH_2$ ,  $-NHZ_1$ ,  $-NZ_1Z_2$ ,  $-C(=NH)NH_2$ ,  $-C(=NOH)NH_2$ ,  $-N$ -morpholino, and  $-S(O)_m(CF_2)_qCF_3$ , wherein  $m$  is 0, 1 or 2,  $q$  is an integer from 0 to 5, and  $Z_1$  and  $Z_2$  are independently selected from the group consisting of alkyl of 1 to about 12 carbon atoms, aryl of about 6 to about 14 carbon atoms, heteroaryl of 5 to about 14 ring atoms, aralkyl of 7 to 15 carbon atoms, and heteroaralkyl of 5 to about 14 ring atoms, or

(ii)  $Y_1$  and  $Y_2$  are selected together to be  $-O[C(Z_3)(Z_4)]_rO$  or  $-O[C(Z_3)(Z_4)]_{r+1}-$ , wherein  $r$  is an integer from 1 to 4 and  $Z_3$  and  $Z_4$  are independently selected from the group consisting of hydrogen, alkyl of 1 to about 12 carbon atoms, aryl of about 6 to about 14 carbon atoms, heteroaryl of about 5 to about 14 ring atoms, aralkyl of about 7 to about 15 carbon atoms, and heteroaralkyl of about 5 to about 14 ring atoms;

(c)  $R_2$  is hydrogen or alkyl of 1 to 12 carbon atoms;

(d)  $n$  is 0, 1, 2 or 3;

(e)  $R_3$  is hydrogen or methyl or  $R_3$ ,  $R_{4a}$  and  $q$  are selected together as set forth in (g);

(f)  $R_{4a}$  and  $R_{4b}$  are independently hydrogen, lower alkyl of 1 to 3 carbon atoms, and  $q$  is 0, 1 or 2, or  $R_3$ ,  $R_{4a}$  and  $q$  are selected together as set forth in (g);

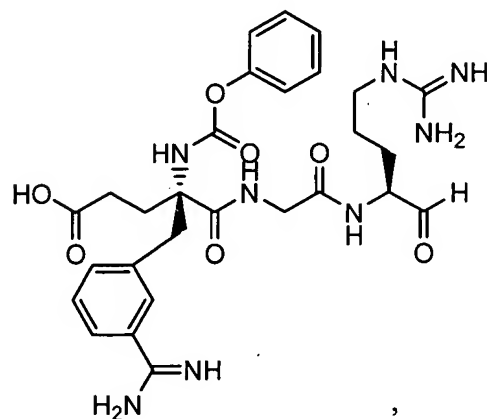
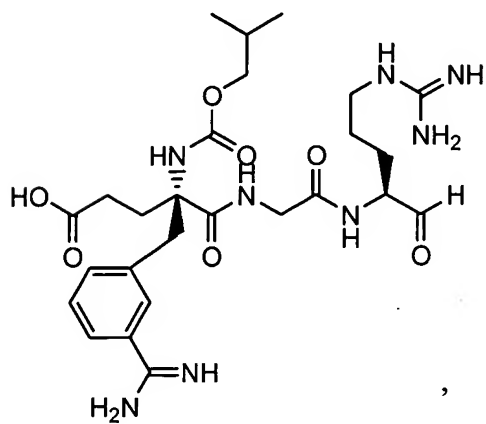
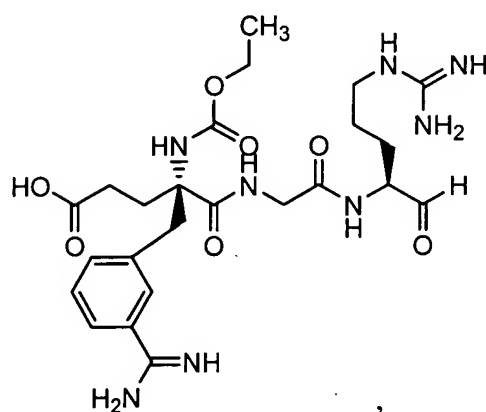
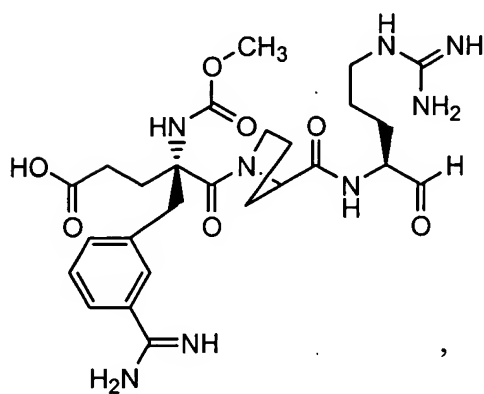
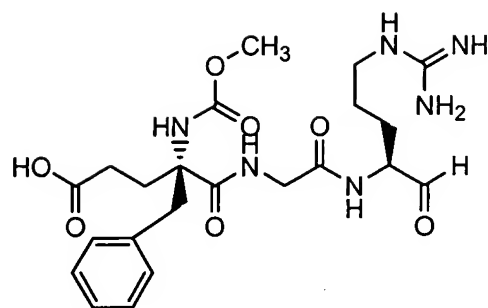
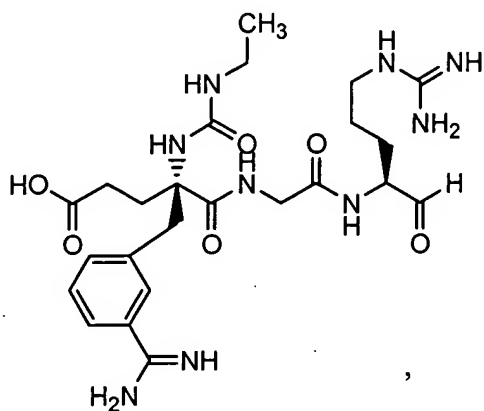
(g)  $q$  is 0 and  $R_3$  and  $R_{4a}$  are selected together to be in the S-configuration to give a group at P2 selected from the group consisting of prolyl, pipecolyl, azetidine-2-carbonyl; 4-hydroxyprolyl, 3-hydroxyprolyl, 4-aminoprolyl, 4-( $CH_2NH_2$ )-prolyl, 3, 4-methanoprolyl and 3,4-dehydroprolyl;

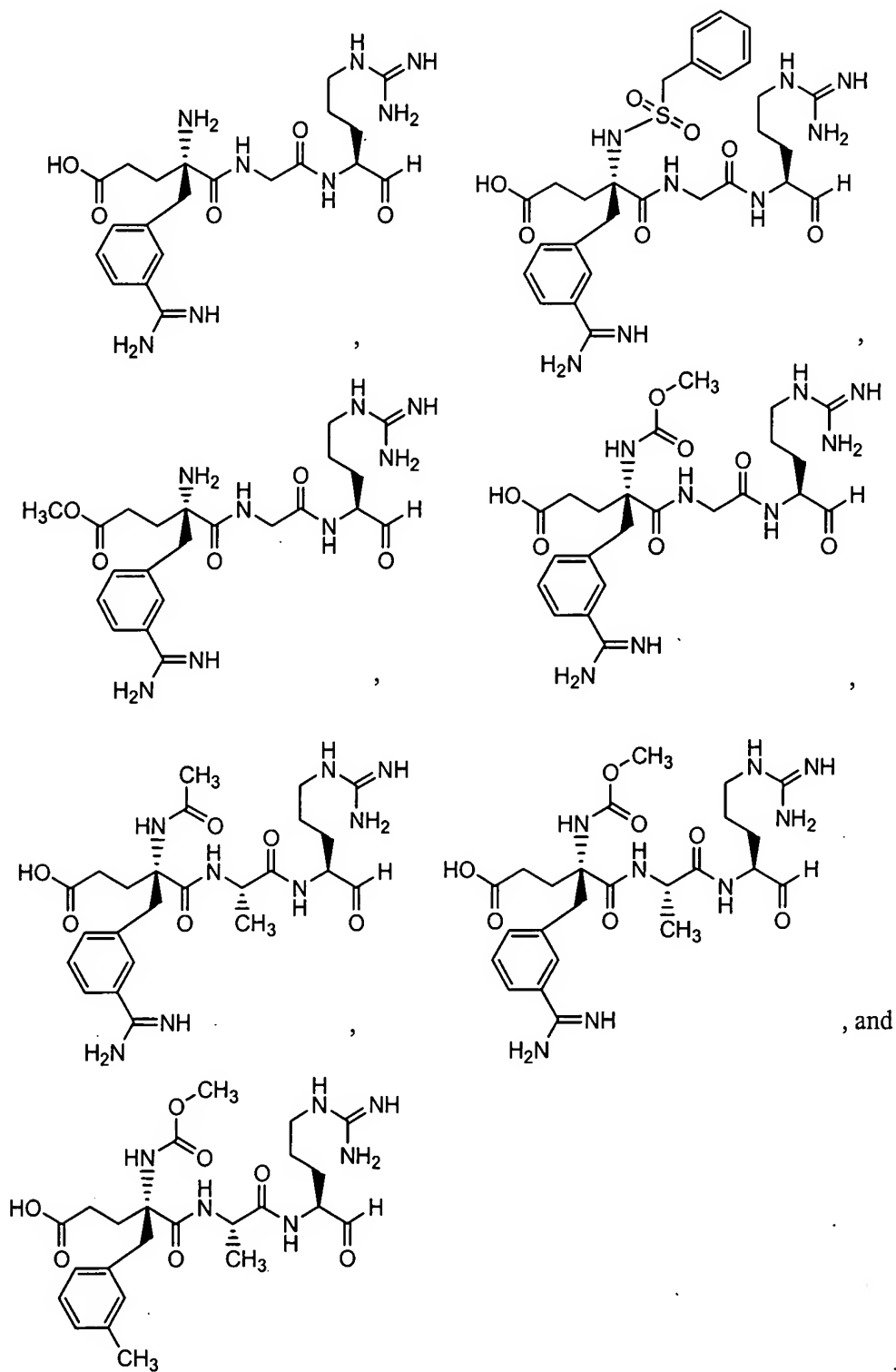
(h)  $E$  is a 5- or 6-membered aromatic ring having 0 to 2 ring heteroatoms and the remainder of the ring atoms carbon atoms, wherein the heteratoms are selected from the group consisting of oxygen, nitrogen and sulfur, and which is substituted with  $R_5$  and  $R_6$  wherein  $R_5$  and  $R_6$  are independently selected from the group consisting of hydrogen, , hydroxy, halogen, alkyl of 1 to about 6 carbon atoms, alkyl of 1 to about 4 carbon atoms substituted with alkoxy of 1 to about 4 carbon atoms, alkoxy of 1 to about 6 carbon atoms and trifluoromethyl; and

(i) T is hydrogen, hydroxy,  $-\text{CH}_2\text{OH}$ , alkyl of 1 to about 3 carbon atoms, cyano,  $-\text{C}(=\text{NR}_7)\text{NHR}_8$ ,  $-\text{NH}-\text{C}(=\text{NR}_7)\text{NHR}_8$ ,  $-\text{NHR}_9$ , or  $-\text{C}(=\text{O})\text{NHR}_9$  wherein  $\text{R}_7$  and  $\text{R}_8$  are independently hydrogen, hydroxy, alkoxy of 1 to about 3 carbon atoms, trihydrocarbosilyl of 3 to about 16 carbon atoms, alkyl of 1 to about 3 carbon atoms or  $-\text{C}(=\text{O})\text{R}_9$  wherein  $\text{R}_9$  is hydrogen, alkyl of 1 to about 6 carbon atoms, alkoxy of 1 to about 6 carbon atoms or  $-(\text{CF}_2)_j\text{CF}_3$  wherein  $j$  is 0, 1, 2 or 3, and with the proviso that  $\text{R}_7$  and  $\text{R}_8$  are not both hydroxy or alkoxy; and pharmaceutically acceptable salts thereof.

2. (Original) A compound according to claim 1 wherein  $q$  is 0.
3. (Original) A compound according to claim 2 wherein  $n$  is 0 or 1.
4. (Original) A compound according to claim 3 wherein  $\text{R}_3$  is hydrogen.
5. (Original) A compound according to claim 4 wherein  $\text{R}_{4a}$  is hydrogen or methyl.
6. (Original) A compound according to claim 5 wherein  $\text{R}_2$  is hydrogen or methyl.
7. (Original) A compound according to claim 6 wherein  $X$  is a direct link,  $-\text{S}(\text{O})_2-$ ,  $-\text{C}(=\text{O})\text{O}-$ , or  $-\text{C}(=\text{O})\text{NH}-$ .
8. (Withdrawn) A compound according to claim 7 wherein  $X$  is a direct link.
9. (Withdrawn) A compound according to claim 8 wherein  $\text{R}_1$  is hydrogen.
10. (Withdrawn) A compound according to claim 7 wherein  $X$  is  $-\text{S}(\text{O})_2-$ .
11. (Withdrawn) A compound according to claim 10 wherein  $\text{R}_1$  is aralkyl.
12. (Original) A compound according to claim 7 wherein  $X$  is  $-\text{C}(=\text{O})\text{O}-$ .
13. (Original) A compound according to claim 12 wherein  $\text{R}_1$  is alkyl.

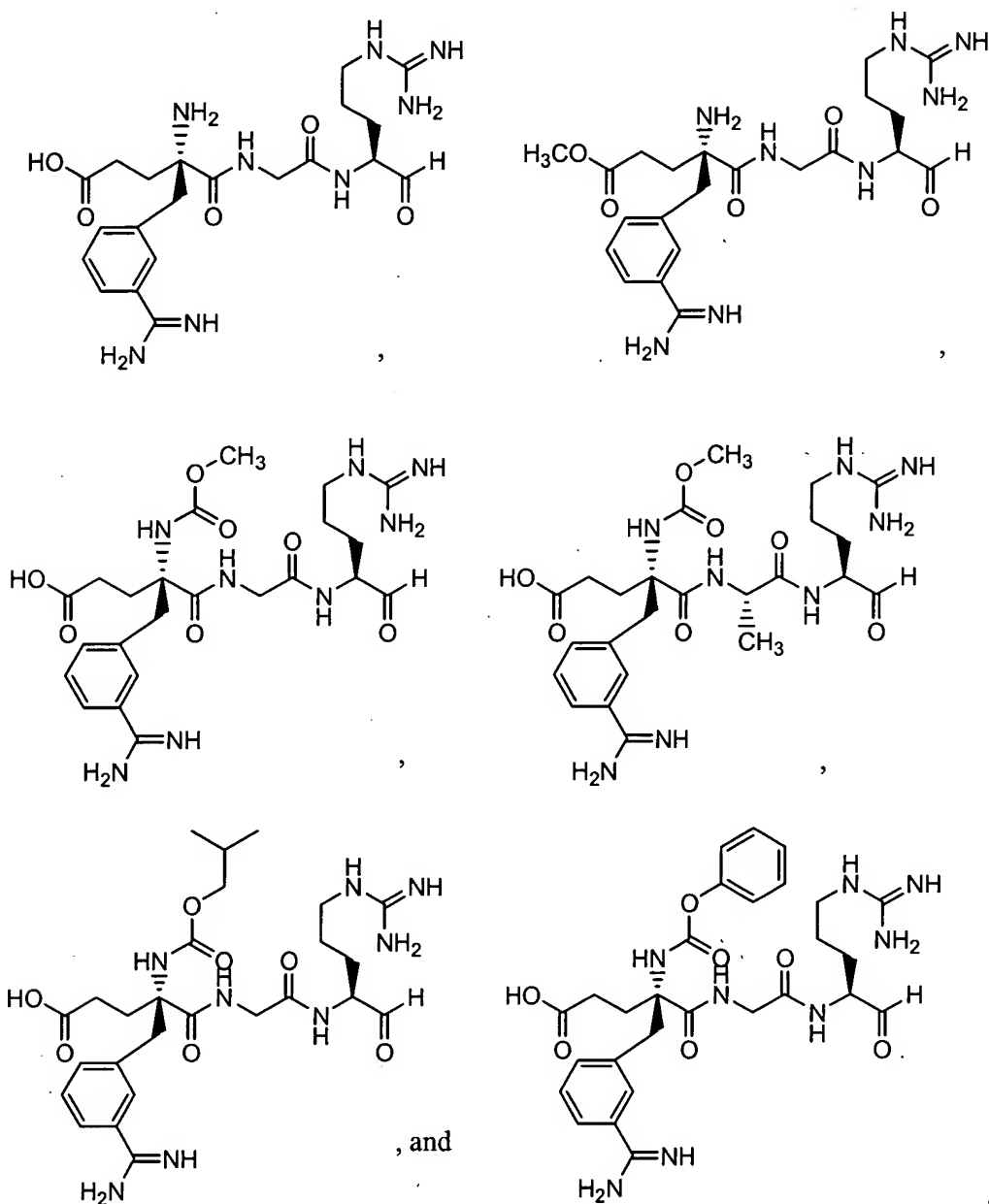
14. (Original) A compound according to claim 7 wherein E is phenyl.
15. (Original) A compound according to claim 14 wherein T is -  
 $C(=NR_7)NHR_8$ .
16. (Original) A compound according to claim 15 wherein  $R_7$  and  $R_8$  are hydrogen.
17. (Withdrawn) A compound according to claim 3 wherein  $R_3$  and  $R_{4a}$  are selected together as set forth in (g) of claim 1.
18. (Original) A compound according to claim 2 wherein E is phenyl.
19. (Withdrawn) A compound according to claim 18 wherein X is a direct link and  $R_1$  is hydrogen.
20. (Withdrawn) A compound according to claim 19 wherein  $R_2$  is hydrogen or alkyl of 1 to about 3 carbons.
21. (Original) A compound according to claim 18 wherein T is - $C(=NR_7)NHR_8$ .
22. (Original) A compound according to claim 21 wherein  $R_7$  and  $R_8$  are hydrogen.
23. (Original) A compound according to claim 1 wherein E is phenyl.
24. (Withdrawn) A compound according to claim 23 wherein  $R_3$  and  $R_{4b}$  are hydrogen and  $R_{4a}$  is hydrogen or methyl or q,  $R_3$  and  $R_{4a}$  are taken together as in (g) of claim 1.
25. (Previously presented) A compound according to claim 1 selected from the group consisting of:







26. (Previously presented) A compound according to claim 1 selected from the group consisting of:



27. (Previously presented) A pharmaceutical composition which comprises an amount effective to inhibit or decrease serine protease activity of matriptase or MTSP1 of a compound of any of claims 1 to 26.

28. (Original) A method of treating a pathologic condition in a mammal which is ameliorated by decreasing or inhibiting the serine protease activity of

matriptase or MTSP1 which comprises administering to said mammal an amount of a compound of any of claims 1 to 26 effective to decrease or inhibit serine protease activity of matriptase of MTSP1.

29. (Original) A method of treating a pathologic condition in a mammal which is ameliorated by decreasing or inhibiting the serine protease activity of matriptase or MTSP1 which comprises administering to said mammal an amount of a composition of claim 27 effective to decrease or inhibit serine protease activity of matriptase of MTSP1.

30. (Currently amended) A method of treating a condition which is ameliorated by inhibiting or decreasing serine protease activity of matriptase or MTSP1 in a mammal which comprises administering to said mammal an therapeutically effective amount of a compound of any of claims 1 to 26 ~~which inhibits serine protease activity of matriptase of MTSP1.~~

31. (Original) A method according to claim 30 wherein said compound has an IC<sub>50</sub> of 100 nM or less.

32. (Cancel).

33. (Currently amended) A method of treating a condition which is ameliorated by inhibiting or decreasing serine protease activity of matriptase or MTSP1 in a mammal in need of treatment which comprises administering to said mammal a therapeutically effective amount of a compound of any of claims 1 to 26 ~~which selectively inhibits serine protease activity of matriptase or MTSP1.~~

34. (Cancel).

35. (Cancel).

36. (Cancel).